REMARKS

Claims 25-30 are pending in this application. Applicant respectfully requests consideration of the remarks made below.

Information Disclosure Statement

The Examiner has refused to consider document C7 because the search report citing document C7 is directed to a PCT application that does not have the same claims as the pending application. Applicant directs the Examiner's attention to CFR §1.98(a)(3) and the MPEP at section 609(III)(A)(3) which provides that a statement of relevance of a foreign language document does not need to be provided to the Examiner if the document was cited in a related foreign application and the applicant provides the Examiner with an English language search report indicating the relevance of the document. Applicant respectfully submits that the PCT application is a related foreign application. The noted PCT application and the present application are identical and the present application had the same claims as the PCT application at the time of filing. Applicant has attached a copy of the PCT application and the A3 publication of the search report for the Examiner's review. Applicant again requests that the Examiner consider document C7.

35 U.S.C. §103(a)

Claim 25

The Examiner rejected Claim 25 under 35 U.S.C. §103(a) as being obvious over Frisch.

To establish a prima facie case of obviousness under 35 U.S.C.§103, the Examiner must demonstrate that, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. Further, the prior art must provide one of ordinary skill with a reasonable expectation of success. M.P.E.P. §2143.

Additionally, the prior art references must be enabling. "In order to render a claimed apparatus of method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

Claim 25 is directed toward a composition comprising colchicine ((S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)acetamide) and cisplatin wherein the modulation of a cellular proliferative disease by colchicine and cisplatin is greater than the sum of the modulation for colchicine and cisplatin when administered alone. Claim 25 has been amended in this Response to reflect the fact that the modulation of a cellular proliferative disease with colchicine and cisplatin is greater than the sum of the modulation for colchicine and cisplatin when administered alone. Support for this amendment can be found in Example 3 of the specification.

Frisch teaches use of the adenovirus E1A to sensitize human tumor cells to chemotherapy or irradiation. Frisch provides a list of chemotherapeutic agents including colchicine, cisplatinum, etopside, camptothecin, and vinblastine. However, Frisch does not teach a combination of the chemotherapeutic agents. The Examiner relies on Abe, Earle and Furue to show that combination therapies, including combining cisplatin with other drugs, was known in the art. The Examiner concludes by stating that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients.

However, "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...." MPEP §716.02(a) citing *In re Corkhill,* 711 F.2d 1496 (Fed. Cir. 1985). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of the effects taken separately. MPEP §716.02(a). Thus, a showing of unexpected synergism between individual components may be used to show that an invention is not obvious over art related to individual components. Applicant directs the Examiner's attention to Example 3 of the instant specification, including Figure 6. Example 3 sets forth the data obtained when treating tumor cells with colchicine alone, cisplatin alone, and with a combination of colchicine and cisplatin. As illustrated in Table 8 and Figure 6, the effect on the growth of tumors treated with a combination of colchicine and cisplatin is more than additive over the effect on the growth of tumors treated with colchicine or cisplatin alone. One of skill in the art would reasonably expect that, at best, the combination of colchicine and cisplatin would result in a delay in tumor growth of 1.47 days which is the additive effect of the colchicine and the cisplatin treatments (0.02 days (the delay provided by treatment with colchicine) + 1.45 days (the delay provided by treatment with cisplatin)). However, the combined treatment using colchicine and cisplatin resulted in a delay of 3.59 days. None of the references cited by the Examiner provides a reasonable expectation that

the combination of colchicine with cisplatin would produce an effect that is more than additive over the individual components. As such, Applicant submits that claim 25 directed toward a combination of colchicine and cisplatin is not obvious over Frisch in view of Abe, Earle and Furue and requests withdrawal of the rejection.

Claims 25-29

The Examiner rejected Claims 25-29 under 35 U.S.C. §103(a) as being obvious over Frisch and Bombardelli.

Claim 25 is directed toward a composition comprising colchicine ((S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)acetamide) and cisplatin wherein the modulation of a cellular proliferative disease by colchicine and cisplatin is greater than the sum of the modulation for colchicine and cisplatin when administered alone. Claim 25 has been amended in this Response to reflect the fact that the modulation of a cellular proliferative disease with colchicine and cisplatin is greater than the sum of the modulation for colchicine and cisplatin when administered alone.

Frisch teaches use of the adenovirus E1A to sensitize human tumor cells to chemotherapy or irradiation. Frisch provides a list of chemotherapeutic agents including colchicine, cisplatinum, etopside, camptothecin, and vinblastine. However, Frisch does not teach a combination of the chemotherapeutic agents.

Bombardelli teaches novel colchicine derivatives. Bombardelli refers to colchicine in the background of the invention as a compound useful in treating gout and that colchicine is a potent antiblastic agent. Bombardelli does not teach a composition comprising colchicine in combination with an additional agent with antiproliferative properties. Neither does Bombardelli discuss the desirability of combining colchicine with other antiproliferative agents.

As discussed in the above section "Claim 25", Frisch does not provide a reasonable expectation that the combination of colchicine with cisplatin would produce an effect that is more than additive over the individual components. Likewise, Bombardelli does not provide any evidence that the combination of colchicine and cisplatin would have a more than additive effect over

colchicine and cisplatin used alone. As such, claim 25 directed toward a combination of colchicine and cisplatin is not obvious over Frisch and Bombardelli.

Claim 26-29 are directed toward a composition comprising thiocolchicoside in combination with cisplatin (Claim 26) , a composition comprising thiocolchicoside in combination with etoposide (Claim 27) , a composition comprising thiocolchicoside in combination with camptothecin (Claim 28) , and a composition comprising thiocolchicoside in combination with vinblastine (Claim 29).

The Examiner cites to the abstract and the first column (Background Arts) from Bombardelli for the assertion that Bombardelli teaches that colchicine and thiocolchicoside have antiproliferative activity and are cytotoxic to tumor cells. Applicant respectfully disagrees with this analysis. Bombardelli discloses that colchicine is an antiblastic agent (see Column 1, lines 20-21). However, Bombardelli refers to thiocolchicoside only as a compound used to treat contractures and inflammatory conditions on skeletal muscles (see Column 1, lines 18-20). Contrary to the Examiner's analysis, Bombardelli does not disclose that thiocolchicoside possesses antiblastic or antitumor properties. In fact, Bombardelli attributes these properties exclusively to colchicine. Additionally, Bombardelli discloses that only one colchicine derivative, demecolcine, is used in oncology (see Column 1, lines 28-30). One of skill in the art reading Bombardelli would find no motivation to combine thiocolchicoside with an antiproliferative agent such as those listed in claims 26-29. As such, Bombardelli does not make obvious a composition comprising thiocolchicoside in combination with cisplatin, etoposide, camptothecin, or vinblastine.

The addition of the Abe, Earle and Furue references to show that combination therapies, including combining cisplatin with other drugs, was known in the art does not change the analysis. None of these references suggest the use of thiocolchicoside in combination with other agents.

Applicant submits that claims 25-29 are not obvious over Frisch and Bombardelli and requests withdrawal of the rejection.

Claims 27 and 29

The Examiner rejected Claims 27 and 29 under 35 U.S.C. §103(a) as being obvious over Bombardelli and Houghton.

Claim 27 recites a composition comprising thiocolchicoside (2-demethoxy-2-glucosidoxythiocolchicine) and etoposide wherein the modulation of a cellular proliferative disease by thiocolchicoside and etoposide is greater than that for thiocolchicoside or etoposide alone.

Claim 29 recites a composition comprising thiocolchicoside (2-demethoxy-2-glucosidoxythiocolchicine) and vinblastine wherein the modulation of a cellular proliferative disease by thiocolchicoside and vinblastine is greater than that for thiocolchicoside or vinblastine alone.

As discussed above in the section designated "Claims 25-29" , Bombardelli does not disclose that thiocolchicoside possesses antiblastic or antitumor properties. In fact, Bombardelli attributes these properties exclusively to colchicine. Additionally, Bombardelli discloses that only one colchicine derivative, demecolcine, is used in oncology. One of skill in the art reading Bombardelli would find no motivation to combine thiocolchicoside with etoposide, as recited in Claim 27, or vinblastine, as recited in Claim 29.

Houghton teaches the use of a potentiating agent, wherein the potentiating agent is a derivative of phenoxazine, to increase the uptake of cytotoxic agents, including colchicine, vinblastine, etoposide. Houghton does not teach a combination of the cytotoxic agents. The combination of Bombardelli with Houghton does not teach or suggest a composition comprising thiocolchicoside in combination with etoposide or vinblastine. As such, Claims 27 and 29 are not obvious over the combination of Bombardelli with Houghton.

The addition of the Abe, Earle and Furue references to show that combination therapies, including combining cisplatin with other drugs, was known in the art does not change the analysis. None of these references suggest the use of thiocolchicoside in combination with other agents.

Applicant requests the rejection be withdrawn.

Claims 27 - 29

The Examiner rejected Claims 27-29 under 35 U.S.C. §103(a) as being obvious over Bombardelli and Ratain.

Claim 27-29 are directed toward a composition comprising thiocolchicoside in combination with etoposide (Claim 27) , a composition comprising thiocolchicoside in combination with camptothecin (Claim 28) , and a composition comprising thiocolchicoside in combination with vinblastine (Claim 29).

As discussed above in the section designated "Claims 25-29" , Bombardelli does not disclose that thiocolchicoside possesses antiblastic or antitumor properties. In fact, Bombardelli attributes these properties exclusively to colchicine. Additionally, Bombardelli discloses that only one colchicine derivative, demecolcine, is used in oncology. One of skill in the art reading Bombardelli would find no motivation to combine thiocolchicoside with etoposide, as recited in Claim 27, camptothecin, as recited in Claim 28, or vinblastine, as recited in Claim 29.

Ratain teaches the use compounds to reduce the toxicity of camptothecin derivatives such as irinotecan (CPT-11). Example 24 of Ratain provides a list of compounds, including vinblastine, colchicine and etoposide that may find use in combination with irinotecan. Combinations comprising thiocolchicoside are not mentioned in Ratain. Thus, Ratain does not teach or suggest combining thiocolchicoside with etoposide, as recited in Claim 27, camptothecin, as recited in Claim 28, or vinblastine, as recited in Claim 29.

For the reasons above, the combination of Bombardelli with Ratain does not teach or suggest a composition comprising combining thiocolchicoside with etoposide, as recited in Claim 27, camptothecin, as recited in Claim 28, or vinblastine, as recited in Claim 29.

The addition of the Abe, Earle and Furue references to show that combination therapies, including combining cisplatin with other drugs, was known in the art does not change the analysis. None of these references suggest the use of thiocolchicoside in combination with other agents.

Applicant requests the rejection be withdrawn.

Claim 30

The Examiner rejected Claim 30 under 35 U.S.C. §103(a) as being obvious over Bombardelli and Joseph.

Claim 30 is directed toward a composition comprising thiocolchicoside (2-demethoxy-2-glucosidoxythiocolchicine) and paclitaxel wherein the modulation of a cellular proliferative disease by thiocolchicoside and paclitaxel is greater than that for thiocolchicoside or paclitaxel alone.

As discussed above in the section designated "Claims 25-29" , Bombardelli does not disclose that thiocolchicoside possesses antiblastic or antitumor properties. In fact, Bombardelli attributes these properties exclusively to colchicine. Additionally, Bombardelli discloses that only one colchicine derivative, demecolcine, is used in oncology. One of skill in the art reading Bombardelli would find no motivation to combine thiocolchicoside with paclitaxel as recited in Claim 30.

Joseph teaches a drug preparation for treating wounds, wherein the preparation consists essentially of a drug carrier, paclitaxel, penicillamine and colchicine. Joseph discloses that paclitaxel is used to treat various cancers. However, Joseph does not teach or suggest combining thicolchicoside with paclitaxel.

For the reasons above, the combination of Bombardelli and Joseph does not teach or suggest a composition comprising combining thiocolchicoside with paclitaxel as recited in Claim 30.

The addition of the Abe, Earle and Furue references to show that combination therapies, including combining cisplatin with other drugs, was known in the art does not change the analysis. None of these references suggest the use of thiocolchicoside in combination with other agents.

Applicant requests the rejection be withdrawn.

Conclusion

Applicant respectfully requests that the present remarks be considered and submits that the claims are in condition for allowance. An early notification of such is requested . The Examiner is invited to call the undersigned attorney for discussion of any outstanding issues.

Respectfully submitted,

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Date June 29, 2004

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